# SnapShot : Angiopoietins and Their Functions

Saharinen, Pipsa

2017-10-19

Saharinen , P , Leppanen , V-M & Alitalo , K 2017 , ' SnapShot : Angiopoietins and Their Functions ' , Cell , vol. 171 , no. 3 , pp. 724-+ . https://doi.org/10.1016/j.cell.2017.10.009

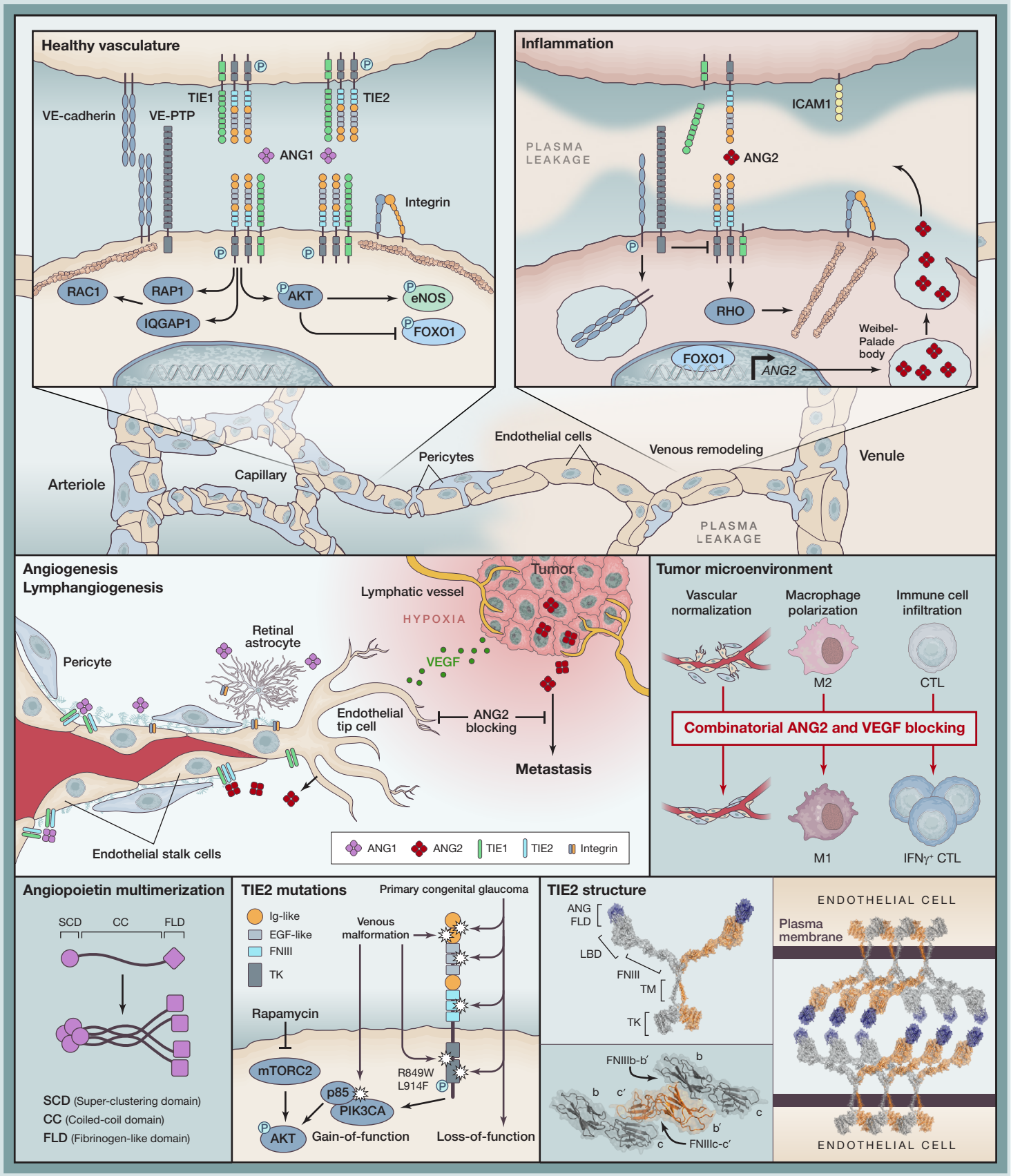
http://hdl.handle.net/10138/298085
https://doi.org/10.1016/j.cell.2017.10.009

publishedVersion

# SnapShot: Angiopoietins and Their Functions

Pipsa Saharinen, Veli-Matti Leppänen, Kari Alitalo
University of Helsinki and Wihuri Research Institute, 00290 Helsinki, Finland

Cell




 DOI http://dx.doi.org/10.1016/j.cell.2017.10.009

See online version for legends and references

# SnapShot: Angiopoietins and Their Functions

Cell

Pipsa Saharinen, Veli-Matti Leppänen, Kari Alitalo
University of Helsinki and Wihuri Research Institute, 00290 Helsinki, Finland

## Angiopoietins—Major Functions

The angiopoietin growth factors (ANG1-4) bind to endothelial TIE2 receptor tyrosine kinase, which, together with ligandless TIE1 receptor, forms the ANG-TIE signaling complex essential for cardiovascular development and for venous and lymphatic vascular remodeling in an organotypic manner (Augustin and Koh, 2017). ANG2 expression is increased in several human diseases associated with vascular dysfunction, such as sepsis, cancer, diabetes, major traumas, malaria, and viral hemorrhagic fever (Saharinen et al., 2017).

## Angiopoietin Signaling in Vessel Stability and Inflammation

ANG1 stabilizes newly formed vessels, and ANG1 delivery normalizes vessel function in various murine disease models, alleviating disease pathogenesis in oxygen-induced retinopathy, choroidal neovascularization, diabetic nephropathy, systemic inflammation, sepsis, and cardiac allograft transplantation (Saharinen et al., 2017). ANG1 stimulates TIE2 phosphorylation and translocation to endothelial cell (EC)–EC junctions (Korhonen et al., 2016), which improves EC barrier function by stimulating VE-cadherin expression and by stabilizing the cortical actin cytoskeleton (Frye et al., 2015). ANG1 activates the AKT serine kinase, increasing EC survival and phosphorylation of forkhead box transcription factor O1 (FOXO1), leading to decreased expression of FOXO1-targets (Kim et al., 2016; Korhonen et al., 2016). AKT also activates the endothelial nitric oxide synthase 3 (eNOS), which has vascular protective functions. TIE2 dephosphorylation is catalyzed by the hypoxia-inducible vascular endothelial protein tyrosine phosphatase (VE-PTP) (Frye et al., 2015). TIE1 is activated by angiopoietins in a TIE2-dependent manner, and ANG-induced TIE2 activation and vessel remodeling are impaired in mice conditionally deleted of *Tie1* (Korhonen et al., 2016)—ANG1-TIE2 signaling thus stabilizes the vasculature against pathological insults.

In inflammation, ANG2 is released from EC Weibel-Palade bodies, the TIE1 ectodomain is cleaved, and ANG2 switches from a weak TIE2 agonist to an antagonist, contributing to the loss of the integrity of EC junctions and increased plasma leakage from the microvasculature. Similarly, ANG2 agonist activity is lost when *Tie1* is conditionally deleted from the vascular endothelium. ANG2 antagonism of TIE2 phosphorylation activates FOXO1 and induces *Ang2* gene transcription via a positive feedback loop (Kim et al., 2016; Korhonen et al., 2016), whereas ANG1 and TIE2 expression are decreased. When EC TIE2 is decreased, ANG2 destabilizes the endothelium via signaling through integrins, the RHO GTPase, and actin stress fibers (Saharinen et al., 2017). Thus, increased ANG2 and decreased ANG1, TIE2, and TIE1 impair vascular stability in inflammation.

## Angiopoietin-TIE Pathway as a Disease Target

In sprouting angiogenesis, endothelial tip cells express ANG2, but low levels of TIE2, favoring ANG signaling via integrins, whereas in stalk cells, TIE1 and TIE2 co-operate to sustain ANG1 signaling for vascular maturation. In postnatal retina, ANG1 stimulates angiogenesis also via integrins in retinal astrocytes. In tumors, ANG2 expression is associated with vessel destabilization and the angiogenic switch. Drugs that block ANG2 decrease lymphatic and blood vessel growth and are in clinical development for cancer and ocular neovascular diseases. ANG2 targeted drugs inhibit tumor metastasis by normalizing tumor vessels and by interfering with TIE2 expressing proangiogenic M2 macrophages (Saharinen et al., 2017). A combination of VEGF and ANG2 blocking drugs alter the inflammatory tumor microenvironment via macrophage polarization and can boost anti-tumor immunity and immunotherapy (Peterson et al., 2016; Schmittnaegel et al., 2017). Also TIE2 activating agents, including the ABTAA antibody and the VE-PTP inhibitor AKB-9778, can normalize leaky blood vessels in inflammation and in pathological angiogenesis (Saharinen et al., 2017).

## Structural Aspects of ANG-TIE Complexes

Angiopoietins consist of the TIE2 binding carboxy-terminal fibrinogen-like domain (FLD), a coiled-coil domain (CC) for dimerization, and an amino-terminal supercluster-ing domain (SCD) for multimerization. TIE2 (or downstream *PIK3CA*) mutations (examples shown in the figure) cause venous malformations (Saharinen et al., 2017), whereas heterozygous TIE2 inactivating mutations cause primary congenital glaucoma (PCG), an important cause of visual impairment and blindness worldwide (Souma et al., 2016).

The TIE2 ligand binding domain (LBD) consists of immunoglobulin-like and EGF homology domains. Homotypic interactions between the membrane-proximal fibronectin-like type III (FNIII) domains mediate ligand-induced TIE2 *in cis* dimerization and clustering. In TIE2 dimers, the LBDs are located about 300 Å apart from each other (Leppänen et al., 2017; Moore et al., 2017). Multimeric ANG1 can span these sites, whereas dimeric ANG2 cannot, resulting in inefficient TIE2 activation. Further receptor clustering may occur via ANG-mediated TIE *in trans* interactions across EC-EC junctions.

## REFERENCES

Augustin, H. G. and Koh, G. Y. (2017). Science *357*, eaal2379.

Frye, M., Dierkes, M., Küppers, V., Vockel, M., Tomm, J., Zeuschner, D., Rossaint, J., Zarbock, A., Koh, G.Y., Peters, K., et al. (2015). J. Exp. Med. *212*, 2267–2287.

Kim, M., Allen, B., Korhonen, E.A., Nitschké, M., Yang, H.W., Baluk, P., Saharinen, P., Alitalo, K., Daly, C., Thurston, G., and McDonald, D.M. (2016). J. Clin. Invest. *126*, 3511–3525.

Korhonen, E.A., Lampinen, A., Giri, H., Anisimov, A., Kim, M., Allen, B., Fang, S., D'Amico, G., Sipilä, T.J., Lohela, M., et al. (2016). J. Clin. Invest. *126*, 3495–3510.

Leppänen, V.M., Saharinen, P., and Alitalo, K. (2017). Proc. Natl. Acad. Sci. USA *114*, 4376–4381.

Moore, J.O., Lemmon, M.A., and Ferguson, K.M. (2017). Proc. Natl. Acad. Sci. USA *114*, 4382–4387.

Peterson, T.E., Kirkpatrick, N.D., Huang, Y., Farrar, C.T., Marijt, K.A., Kloepper, J., Datta, M., Amoozgar, Z., Seano, G., Jung, K., et al. (2016). Proc. Natl. Acad. Sci. USA *113*, 4470–4475.

Saharinen, P., Eklund, L., and Alitalo, K. (2017). Nat. Rev. Drug Discov. *16*, 635–661.

Schmittnaegel, M., Rigamonti, N., Kadioglu, E., Cassará, A., Wyser Rmili, C., Kiialainen, A., Kienast, Y., Mueller, H.J., Ooi, C.H., Laoui, D., and De Palma, M. (2017). Sci. Transl. Med. *9*, eaak9670.

Souma, T., Tompson, S.W., Thomson, B.R., Siggs, O.M., Kizhatil, K., Yamaguchi, S., Feng, L., Limviphuvadh, V., Whisenhunt, K.N., Maurer-Stroh, S., et al. (2016). J. Clin. Invest. *126*, 2575–2587.

  DOI http://dx.doi.org/10.1016/j.cell.2017.10.009